A STUDY OF THE CLINICAL FEATURES OF RENAL PAPILLARY NECROSIS

Jose Luis Martinez

1978

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Date

A STUDY OF THE CLINICAL FEATURES OF RENAL PAPILLARY NECROSIS

Jose Luis Martinez

A Thesis Submitted to the Yale University School of Medicine
in Partial Fulfillment of the Requirements for the Degree of
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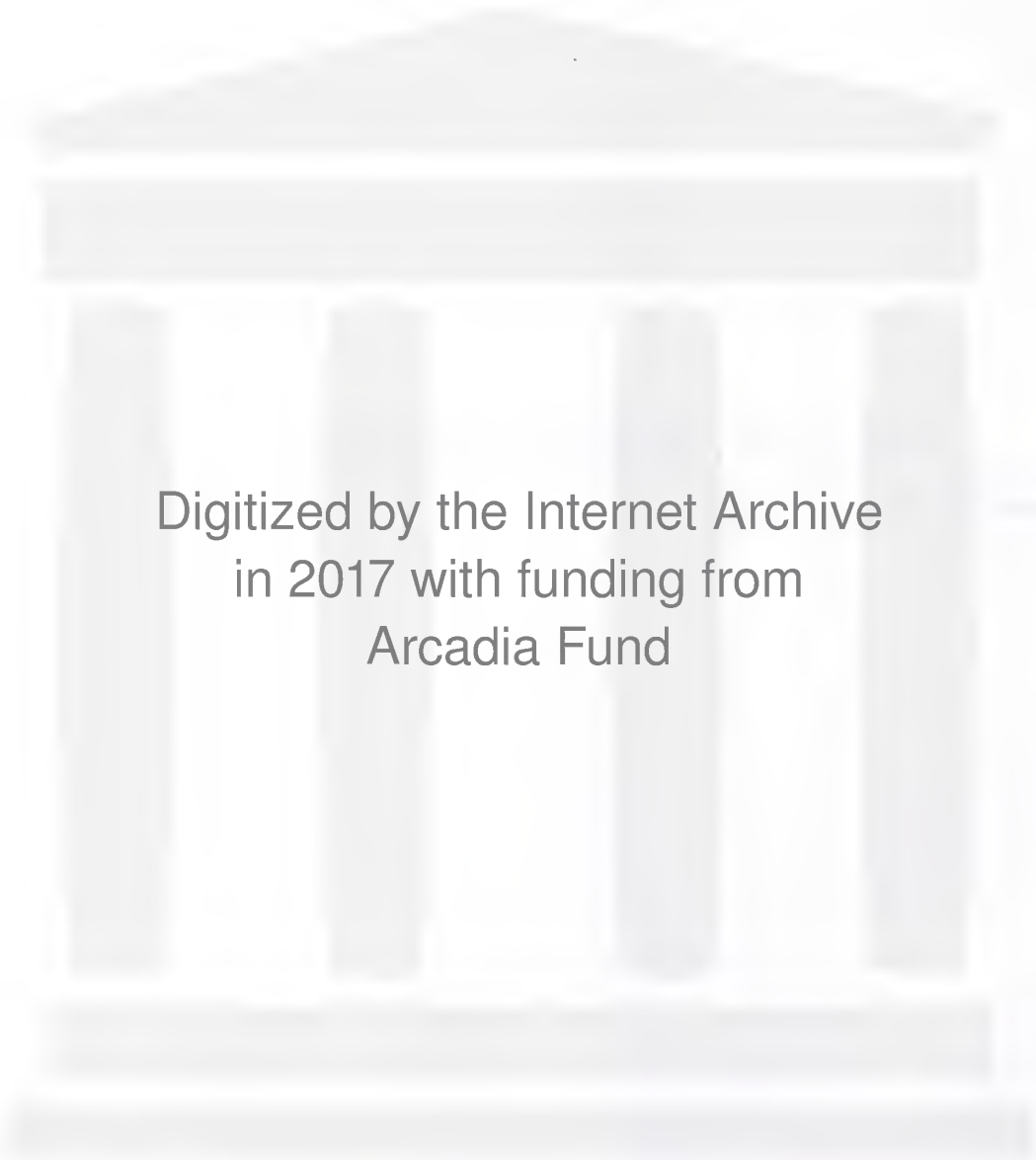
1978

Dedication

A Luis y Fini, quienes son principalmente responsables de mis exitos.



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Introduction

Renal papillary necrosis is a disease entity that has been recognized since 1878. Today, one hundred years later, a considerable amount of knowledge has been gathered about its possible etiologies, associated conditions, pathological picture, clinical manifestations, radiological features and mode of treatment. Very little is known, however, about prognosis of this disease. The literature is deficient of prognostic studies that may help the clinician predict the course of patients with renal papillary necrosis.

This study is aimed to provide some answers to questions in the area of natural history and clinical features of this disease.

Review of the Literature

It was one hundred years ago that Von Friedreich contributed to the medical literature the first description of a case of renal papillary necrosis (84). That first case was observed in association with urinary tract obstruction and hydronephrosis. Since then, this disease entity has been associated with a number of conditions that include most commonly diabetes mellitus, sickle hemoglobinopathies, analgesic abuse and urinary tract obstruction. Most recently the list has been extended to include chronic alcoholism, cirrhosis of the liver, rheumatoid arthritis, ankylosing spondylitis in association with prostaglandin synthetase inhibitors, renal vein thrombosis, renal tuberculosis, aplastic anemia, post gastroenteritis and severe dehydration in infants, histoplasmosis and hypercalcemia with renal failure, and post kidney transplants. It has been reproduced experimentally with agents such as bromoethylamine hydrobromide.

Renal papillary necrosis is generally defined as "an ischemic necrosis involving the renal medulla, which in the absence of localizing, obstructive or vascular factors is usually bilateral and most often associated with infection"(28). Although most investigators are constantly disagreeing with each other about certain issues of pathogenesis and natural history in this

disease, virtually all investigators agree with the first part of this definition--papillary necrosis follows after a vascular lesion has occurred in the renal medulla that compromises the blood supply of the vasa recta. Mechanisms of embarrassment of blood supply in the medulla have been suggested for each of the associated conditions.

There are authors who believe renal papillary necrosis probably represents a variant of pyelonephritis (28, 56, 57). Lauler et al in 1960 presented six case reports and then point out infection as a common denominator (57). Lalli, in 1972, after studying fourteen patients from the Cleveland Clinic who had diabetes mellitus, analgesic abuse, obstructive uropathy and chronic and acute pyelonephritis as contributing factors, observed that urinary tract infection was the most important common finding in his patients (56). Friedenberg states that in patients with papillary necrosis "pyelonephritis is probably the prime etiologic factor, and it is presumed that infection with bacterial proliferation and necrosis leads to decreased blood flow and ischemia" (28). In 1967 Kincaid-Smith, however, showed that papillary necrosis is the primary lesion in the kidney of rats that abuse analgesics (52). Whether papillary necrosis can be taken to represent a variant of pyelonephritis or not is not a crucial issue. More relevant to the clinician should be the fact that the late stages of papillary necrosis may be indistinguishable from chronic

pyelonephritis, as was pointed out by Harrow, who also stresses the importance of identifying the disease early in its course (36).

The pathological lesion in papillary necrosis has been studied with considerable detail. Generally there is a sharp demarcation between necrotic and viable tissue which suggests necrosis due to ischemia. Papillary necrosis is not just an inflammatory process. It is important to point out that the lesion is truly a necrotic one, where the tissue is no longer functional. Davies et al have described three different types of histologic lesions: a large central area of necrosis clearly demarcated from surrounding tissues by a band of leucocytes; a small well demarcated lesion involving the tip of the papillae and a band sclerotic lesion with an indefinite margin (18). Whether there is something specific in the pathogenesis of this disease that determines the type of histologic lesion is not known.

Lagergren et al studied the intrarenal arterial tree in kidneys of patients with papillary necrosis and chronic pyelonephritis using parallel stereo-microangiographic and histologic techniques (55). They found that in the pyramids with fresh papillary necrosis the postglomerular vessels of juxtamedullary glomeruli were not visualized probably due to constriction of the vessels by periglomerular fibrosis. They postulate that if the adaptation of other arteriolae rectae to collaterals fail to

occur, papillary necrosis develops. Harrow entertained the hypothesis of an antigen antibody reaction accounting for vascular blockage which eventually leads to the lesion of papillary necrosis (37). Finally, for each of the conditions that have been associated with this renal lesion, a mechanism of meduallary vascular insufficiency has been hypothesized and many of these are accepted by most investigators as possible in the pathogenesis of the lesion. We will mention these when we consider the literature on each of these associated conditions.

In the last forty years the association of papillary necrosis and diabetes mellitus has been noted many times by different observers. As with the other associated conditions, the indidence of papillary necrosis in diabetes varies with the observer. Harrow reports an 18% incidence in long standing diabetics (36). Prior to 1950, as much as two thirds of all patients with papillary necrosis were diabetics and the remaining third had suffered from obstruction. More recently, most reports note a lower percentage of diabetics, probably due to the wider recognition of this disease as associated with many other conditions together with improvement in diagnostic skills.

The pathogenesis in diabetics is generally accepted to be small vessel disease--arteriolar and arterial sclerosis. Increased vulnerability to infection, increased infection rate and high concentration of glucose in the vasa recta inducing thrombus

formation are also considered contributing factors. Wright, in his paper on an eight year survival of a diabetic with papillary necrosis, lists the autopsy findings: end stage kidneys with hyalinization and fibrosis of glomeruli, dilation of tubules, glomerulosclerosis, arterionephrosclerosis and chronic pyelonephritis (88). He observed no active papillary necrosis but instead, incomplete loss of papillae bilaterally. This description gives us some good insight into the pathology of the diabetic kidney with papillary necrosis. The reputation of diabetes as having the worse prognosis among the different conditions associated with papillary necrosis (1,39,88) probably stems from the observations that the pathology of such kidneys includes more than just necrosis of pyramid tips, but also other renal injuries such as chronic pyelonephritis, arteriolonephrosclerosis and glomerulosclerosis, sometimes leading to end stage kidneys with loss of vital renal function. The cause of death of this particular patient was a right cerebral infarct.

Among the few investigators that have reported on favorable followups of diabetics with papillary necrosis, stands Hugo who presents a case of a diabetic with papillary necrosis diagnosed by histology on tissue passed in the urine who was maintained assymptomatic on bacteriostatic antibiotic therapy with some brief intermissions for sixteen months (44). Nevertheless, the literature points out in general that prolonged survival of diabetics who also

have papillary necrosis is a rare event. Abdulhayoglu, for example, reported in 1964 a study on fourteen such patients of which 13 had died in an eight year period--four of diabetic nephropathy (1). Few of the patients in his study had significant relevant symptoms at diagnosis but most developed characteristic symptoms before death.

Patients who have an S-hemoglobinopathy as an associated condition to papillary necrosis are said to be indistinguishable from patients with other etiologies both radiologically and clinically (24, 38). Renal papillary necrosis has been observed in patients with SS, AS and SC disease, but hematuria has been reported most frequently in patients with AS hemoglobin (21). Various types of papillary abnormalities are seen in as much as 50% of patients with AS hemoglobinopathy (24). Vix reported the first case of a patient with SC hemoglobin and papillary necrosis in 1965 (83). Most likely, the fact that most cases of papillary necrosis have been observed in association with AS hemoglobin rather than with SS or SC is linked to the incidence of the AS disorder itself which is much higher than the SS or SC types (HbSS: HbAS = 1:40).

The most popular mechanism of pathogenisis for sicklers with papillary necrosis is as follows: in the renal medulla factors of high osmolality and low oxygen tension predispose to sickling of red blood cells which occurs in the vasa recta blocking

the blood supply and making the countercurrent mechanism fail which results in hyposthenuria and the anatomical lesion of papillary necrosis (83). Pitcock et al, however, reported a study on early renal changes of patients with SS disease in 1970 on which they show that the lesion is not simply the result of ischemia (75). They studied kidney biopsies of patients with SS disease and hyposthenuria using both light and electron microscopes and noted changes not specific for sickle cell disease--congested glomeruli, minor alterations of foot processes and basement membranes--which were less evident than changes seen in patients with clinical renal disease but more evident than in normals. Whether these early changes in the kidney of the patient with sickle disease are also a result of transient ischemia is not known but certainly possible.

Much has been written about analgesic abuse and its association with renal papillary necrosis and chronic insterititial nephritis. It is a subject matter that has caused much controversy among different investigators that have come up with opposite answers for some basic questions such as--which is the analgesic constituent responsible for the renal damage?, what is the mechanism of pathogenesis involved?, is prognosis really good for those analgesic abusers that abstain once they have some renal damage?.

Unfortunately, the onset of papillary necrosis in analgesic abuse appears to be determined by complex combinations, and no

simple cause-effect relationship has been established for this condition. This apparent complexity begins with the vast number of agents that have been postulated as candidates responsible for causing papillary necrosis: aspirin, phenacetin, N-acetyl-p-aminophenol (APAP, paracetamol), caffeine, amidopyrine, phenazone, phenylbutazone and chemical contaminants in some preparations. Most of the controversy, however, appears to be between those believing ASA is responsible (8,10,29,31,51,71,73,77) and those who blame phenacetin for the renal lesion (14,49,64,74). It has been noted that in North America, the disorder has been associated almost entirely with heavy ingestion of combination products of ASA, phenacetin and caffeine (29). Although there seems to be less clinical and experimental evidence for the nephrotoxicity of single analgesics as compared to that caused by combination drugs, the evidence for renal damage caused by ASA alone is much greater than that for phenacetin alone (29, 51,71,73). Nanra and Kincaid-Smith were able to produce papillary necrosis in seven out of 19 rats given aspirin alone, whereas phenacetin alone failed to cause any renal damage over six to nine months (73). Murray, who studied analgesic nephropathy in 86 patients, observed that 84 patients had abused mixtures containing both ASA and phenacetin, but still note renal papillary necrosis in two patients that had abused aspirin alone (71). Prescott presents another case of a patient with

papillary necrosis who used to ingest seven tablets of ASA per day for three years and who took no preparation containing phenacetin (77). He also suggests that nephrotoxicity has been falsely attributed to phenacetin and that the salicylate usually taken with the phenacetin could very well be responsible for the renal injury. One year ago, Berg et al showed that with increasing plasma levels of ASA there is a decrease in sodium excretion, a dose related decrease in paraaminohypuric (PAH) clearance, and no change in creatinine clearance (18). He implies that ASA inhibits tubular transport mechanism, at least for PAH transport and that the effect of ASA on renal blood flow and sodium excretion may be related to its inhibitory effect on prostaglandin synthesis.

On the other hand, Bluemle et al showed that there is no medullary gradient for salicylate in dehydrated or hydrated dogs whereas there is one for paracetamol, a metabolite of phenacetin, which varies with hydration (10). This kind of evidence points out to phenacetin as responsible for analgesic nephrotoxicity implying the renal accumulation of a toxic metabolite. The author emphasizes that adequate hydration may provide protection in patients who abuse analgesics. However, phenacetin was first implicated in analgesic nephrotoxicity on the basis of being a "common denominator" in most mixtures of analgesics abused by patients that later on developed nephrotoxicity. "This kind of reasoning is reminiscent of the scientist, who, having become in-

toxicated on successive occasions from drinking scotch and soda, bourbon and soda and rye and soda concluded that soda was inebriating" stated Gilman in his editorial in 1964 (31). Kasanen observed that after restriction of the sale of phenacetin in Finland the incidence of papillary necrosis established at autopsy fell from 8.9% to 3.8%. Furthermore, the alternative of both ASA and phenacetin having additive effects in the pathogenesis of analgesic nephropathy and papillary necrosis should also be considered.

The magnitude of the analgesic abuse problem in this country has not been studied accurately, but it is certainly not as common as in foreign countries like Australia and Sweden. Kincaid-Smith states in 1969 that papillary necrosis, the primary lesion of analgesic nephropathy, is 50 times as common in Australia as it is in the United States. Clinical features usually include unexplained renal dysfunction (hyposthenuria, elevated serum creatinine), radiological changes (which include papillary necrosis in situ, ie., without sloughing), sterile pyuria (considered by Dawborn the most frequent urinary finding) and urinary tract symptoms (19,22,61,76). Hare points out that missed diagnosis probably results from lack of awareness of the clinical context of the disease, failure to display calyceal detail in pyelography and ignorance of the frequency of the necrosis in situ type--the other types being total papillary sloughing, which leads to club-

bed calyces, and partial papillary sloughing, which leads to papillary cavities (35).

Kincaid-Smith presented pathological, clinical and radiological data to support her hypothesis for the pathogenesis of the lesion in analgesic abuse: papillary necrosis is the primary lesion and probably results from precipitation of excretion products of analgesic drugs in the highly osmolar medulla; cortical changes are a result of atrophy which develops as a consequence of papillary necrosis (52). Papillary necrosis in analgesic abuse is once again believed to be secondary to an interruption of blood supply in the vasa recta (3,50,53). Investigators like Pribe and Barraclough have discussed mechanisms by which phenacetin may cause papillary necrosis: paracetamol is concentrated in the papillae as a result of the countercurrent supply of blood, probably inhibits cellular enzymes, causes methemoglobinemia, or has a direct toxic effect leading to anoxia or ischemia of the papillae (6,78). Hypersensitivity reaction and the effect of shortened life span of red blood cells have been other possibilities entertained (31). Last year, Abrahams noted changes of hyalinization of vessels in the submucosa of bladder tissue, pelvis, ureter and renal medulla in patients with analgesic nephropathy (4). The suggestion was made that these vascular changes may play an important role in the development of papillary necrosis.

The prognosis in analgesic nephropathy is believed to be good if the drugs are stopped (7,9,51,61,71,80,86). Murray notes that renal function continues to deteriorate if only phenacetin is stopped and ASA continued (71). Linton and Murray have observed that prognosis is favorable even when significant renal failure has already occurred (61,71). Somewhat less optimistic are Wilson and Bell who besides noting significant improvement in some of the patients, followed some who developed terminal renal failure and others that had static or slowly declining renal function (7,86). However, all agree that the likelihood of improvement is increased with cessation of abuse.

Finally, a series of reports are found in the literature which make reference to the analgesic abuse syndrome-analgesic abuse, analgesic nephropathy and peptic ulceration (19,23,30,70, 71). Hypochromic anemia (from GI losses), hypertension, psychosocial disorders, and signs and symptoms of papillary necrosis have all been associated with this clinical picture. Murray points out that patients who abuse analgesics are more likely to have a family history of drug abuse and show some evidence of personality disorder or neurosis (70). These patients are also prone to abuse other drugs and smoke excessively. Emphasis should be placed in the recognition of this clinical presentation.

The association of rheumatoid arthritis and renal papillary necrosis is based on the therapy. Aspirin and phenacetin are

again the agents most mentioned as responsible for the renal damage. Bulger et al studied 42 patients with rheumatoid arthritis and noted renal abnormalities in 22 (13). The only two patients that took phenacetin did not have renal disease and only one patient had not taken large doses of aspirin as therapy for rheumatoid arthritis. Aspirin is again implied here. On the other hand, Burry et al, Macklon et al, and a New Zealand Rheumatism Association Study all assume the position of defendants of aspirin in the treatment of rheumatoid arthritis, stating that aspirin rarely if ever causes analgesic nephropathy when prescribed and taken appropriately for the treatment of rheumatoid arthritis (14,64, 74). Clausen noted an increase in the incidence of papillary necrosis in the autopsies of patients with rheumatoid arthritis in Denmark from the period of 1951-56 to the period of 1957-60 and attributes this to an increase of phenacetin use in Denmark during that time period (16).

We have already discussed chronic pyelonephritis as some authors consider papillary necrosis a variant of this more general, ill defined condition. One of the problems of establishing chronic pyelonephritis as an associated condition is that the term is not yet clearly defined and clinicians, radiologists and bacteriologists all apply different criteria to its diagnosis (12). Mellins, in this respect, gives us a descriptive paper on chronic pyelonephritis and renal papillary necrosis and makes a good

attempt to define chronic pyelonephritis (67). Case reports of papillary necrosis have been presented, however, where chronic pyelonephritis is the only associated condition (42). Although infection might very well be secondary to papillary necrosis instead of being a causative agent, the mechanism of inflammation and edema occluding the vasa recta is generally accepted (28).

Urinary tract obstruction may lead to the lesion of papillary necrosis (84,32). It is though closely linked to chronic pyelonephritis as an associated condition and likewise, it is many times difficult to determine if obstruction is secondary to papillary necrosis (a sloughed papilla may cause obstruction of a ureter) or indeed a causative factor. Harrow reported that there was no increased incidence of papillary necrosis among cases of obstructed ureters (37).

In a prospective study of patients with radiological pyelonephritis, papillary necrosis and obstructive atrophy, Grower observed a five year survival rate (calculated) of 92% for patients with renal papillary necrosis and a 10 year survival rate of 56% (32). The study indicated a benign course for most patients with radiological pyelonephritis. Another interesting finding was that bacteriuria was not associated with deteriorating renal function.

Lourie et al have reported this year on the association of renal papillary necrosis and ankylosing spondylitis (63). All

three patients had received prostaglandin synthetase inhibitors (phenylbutazone, indomethacin, ibuprofen) and the authors postulate that these drugs could have an adverse effect on the blood flow of the renal medulla. A renal vascular lesion related to the ankylosing spondylitis could possibly play a role in pathogenesis here. Also, one of the three patients had AS disease.

Longacre et al have noted cirrhosis of the liver as an associated condition of papillary necrosis (62). The pathogenesis implied here is that the increased total renal vascular resistance noted in patients with cirrhosis reflects renal vasoconstriction with reduced renal blood flow. Thus, ischemic necrosis of the papillae can result from this vasoconstriction and/or thrombosis of the vasa recta. They also note that cirrhotic patients with renal dysfunction share some consistent features such as inability to excrete sodium adequately, hyposthenuria and increased total renal vascular resistance.

Edmondson et al reported on the association of chronic alchoholism and papillary necrosis (25). They studied 20 patients with chronic alcoholism (16 of these 20 had fatty change or cirrhosis of the liver or both) and papillary necrosis out of a total of 195 patients with papillary necrosis. At necropsy, all of these patients had acute pyelonephritis, 12 had cortical abscesses, and 12 had acute cystitis. Their hypothesis for pathogenesis is that the alcoholic is more vulnerable to infection.

Several reports are included in the literature on the association of papillary necrosis and post gastroenteritis and severe dehydration in infants (5,15,45). Dehydration has been implied as playing a most important role in pathogenesis here. Prognosis differs with different reports. Chrispin, for example, notes that renal damage by follow-up IVP's is permanent in these kids and indistinguishable from chronic pyelonephritis (15). Husband, on the other hand, notes a slightly better prognosis than Chrispin--one of his two infants had normal renal growth nine months after the acute episode by IVP whereas the other one could not concentrate the urine still at nine months. Renal tubular necrosis was also noted following severe gastroenteritis and dehydration in these infants.

Wind et al present a case report of a patient with aplastic anemia and papillary necrosis (87). That particular patient died of septicemia and autopsy findings included papillary necrosis, hemosiderosis, and aplastic anemia. The authors state that there is no experimental evidence leading to the association of heavy metal deposition and papillary necrosis. Thus they attribute the renal lesion to the aplastic anemia, again implying ischemia in the pathogenesis.

Walker et al report on a 56 year old man with histoplasmosis, hypercalcemia, renal failure and papillary necrosis (85). The autopsy revealed necrotizing histoplasmosis of the renal medulla

and papillitis.

Renal vein thrombosis constitutes another rare associated condition of papillary necrosis. Swartz et al noted that two out of his seven examples of renal papillary necrosis had renal and intrarenal vein thrombosis as well (81). Trauma with shock (81) and renal tuberculosis (56) must also be mentioned for the sake of completeness.

Papillary necrosis has also been noted in transplanted kidneys (26,59,82). It is believed that the lesion here is part of the acute rejection process. The hypothesis is that immediate formation of microthrombi in the vasa recta leads to papillary ischemia.

This year a case report of a patient with an aberrant renal papilla appeared in the literature (54). The patient was assymptomatic, had negative laboratory tests but an abnormal IVP. A retrograde showed abnormal renal papilla mimicking papillary necrosis. Although this is a rare case, the clinician must be aware and observation should be the treatment of choice.

The lesion of renal papillary necrosis has been reproduced experimentally by a variety of agents including analgesics, vinylamine, bromethylamine hydrobromide (BEA) and human serum. These experiments further confirm that complex mechanisms probably operate in the pathogenesis of this renal lesion. Murray, Wyllie, Hill et al studied the mechanism of BEA induced papillary necrosis (43,69). They noted that the earliest changes to occur are necrosis

of limbs of Henle and eosinophilic droplets in the collecting ducts. They could not demonstrate organic blockage of the vasa recta or capillaries and noted that changes in the vasa recta occur simultaneously with tubular changes. Later on they make the observation that vasoconstriction plays an important role in pathogenesis since reserpine, which depletes catecholamines, had an inhibitory effect on the development of the lesion. Ham and Tange reported on vinylamine induced papillary necrosis (34). They used carbon labelling to detect circulation at different stages of the lesion. They conclude that direct tissue injury and venous circulatory statis are most important in pathogenesis. The experiments with analgesics by Kincaid-Smith have already been mentioned in the section of analgesic abuse.

Very little is found in the literature regarding prognosis of this disease. What is known about prognosis is mostly in connection to the analgesic abuse condition and this has already been mentioned. We also pointed out the bad reputation of diabetes in terms of prognosis, and the five year and 10 year survival rate noted by Gower (32). There is no comprehensive prognostic study found in the literature that considers all the associated conditions in the determination of prognosis.

A few papers appear in the literature on the subject of treatment, mostly in reference to the surgical and urological management (11,27,40,41,48). Most authors agree that treatment should

aim at the correction of the associated condition (ie., stop analgesic abuse), treating infection when it is present and symptomatic treatment. Catheter drainage, open surgical procedures and even unilateral nephrectomy may become necessary to relieve obstruction, prevent sepsis and save renal function.

Methods and Materials

In this study, the hospital charts of 62 patients with renal papillary necrosis were obtained from the Department of Medical Records of the Yale-New Haven Hospital and reviewed. This group of patients was selected from two sources: A- a larger group of 321 patients carrying a diagnosis of pyelonephritis provided by the Medical Records coding system, seen in the years 1969 to 1972, which was then screened for cases of papillary necrosis; and B- a group of patients with positive radiographic changes whose names and unit numbers were provided by Dr. Arthur Rosenfield, radiologist. Nineteen patients were accepted for the study after screening the large number of patients coded under pyelonephritis in the years 1969-1972. The other 43 patients belong to the subgroup provided by the radiologist and whose dates of diagnosis range from 1963 to 1977. All patients included in this study had renal papillary necrosis as diagnosed by positive radiographic changes or pathologic description. Our group is by no means a complete group since we did not intend to include all cases of papillary necrosis diagnosed in the last fifteen years. Neither is our group randomized because of the way that the patients were selected. However, we believe our group of patients represent a large adequate series for the study of the clinical features of this disease. Our findings were analyzed keeping in mind the above

mentioned limitations of patient selection and unnecessary and inaccurate comparisons to the general population were avoided.

The study was undertaken in a retrospective way and an attempt to update information was included. Limitation of time prevented a prospective study, which could have had the advantages of better control in patient selection, completeness of the patient population, uniformity of valuable information obtained, and most important, adequate follow-up for most patients.

A retrospective check list was prepared for the chart review, and it is included here as Appendix 1. Its format was designed for easy transfer of information into IBM computer cards. Thus all answers in our questionnaire are recorded as digits from 0 to 9 in each space, and each space is numbered and corresponds to an IBM computer card location. Each card can hold 80 such locations and our questionnaire took a total of five cards to accommodate all the information.

The following items were looked for in each chart and recorded in the retrospective check list: demographic data (sex, ethnic origin, age); is the patient dead or alive? and cause of death; associated conditions (diabetes mellitus, sickle hemoglobinopathies, analgesic abuse, urinary tract obstruction, chronic pyelonephritis, renal vein thrombosis, alcoholism and cirrhosis); significant medical history (including psychiatric history, hypertension, cigarette smoking and urinary tract infection); method of

diagnosis; findings of urinalysis, BUN, serum creatinine and signs and symptoms at diagnosis and every year after for five years; and modality of treatment employed. A section for current status is included as the last page of the check list. Part I of this section concerns an update of signs and symptoms. For this purpose a questionnaire and an informed consent form was sent to those living patients whose addresses were available from their charts. Of the 52 letters sent, seven questionnaires were returned completed, three were returned because the patients were now deceased and 12 were returned because they were undeliverable as addressed. Our attempt to obtain an update of information in our group of patients was not very successful.

A section for radiographic changes was provided in our retrospective check list and concerned mostly the IVP or retrograde description at diagnosis and every year after for five years, the question of unilateral or bilateral involvement and the number of calyces involved. The descriptions of radiographic studies included in the charts were found to be insufficient in providing the desired information about the radiological findings in this disease. A more extensive and careful survey of the radiographic studies that these patients underwent is being conducted simultaneously by Dr. Arthur Rosenfield. The check list is similar in format to the one used in this study and its data should be easily processed and correlated with our findings by the computers, once the

information is passed to IBM computer cards.

The data gathered from our 62 patients was transferred to computer cards by the A&M Keypunching Services of Yale Computer Center. The program for handling and processing the data was devised using the Data-Text system.

Results

Since this study belongs in the category of non-experimental, descriptive research, statistical tests of significance were not felt to be helpful and, thus, are not included (46). Computer analysis made two-dimensional correlation a relatively easy procedure. Thus, we provide here means and frequency distributions for most variables as these correlate to the entire group of 62 patients and to the patients grouped by associated conditions. Finally, we looked into cross-correlations between some variables and patients with distinctive, interesting features (ie., hypertensives, cigarette smokers, patients with history of urinary tract infection).

Table 1 displays the data that describes our patients demographically in terms of age (including mean age at diagnosis, median age and range), sex and ethnic origin.

We found we could group our 62 patients by associated conditions in two different ways: A- where each patient had only one associated condition, and if the patient had more than one he was placed in the "mixed etiologies" group (distribution of patients in this manner is--81% (5) diabetics alone, 9.7% (6) S-hemoglobinopathy patients, 1.6% (1) analgesic abuser, 9.7% (6) urinary tract obstruction patients, 3.2% (2) chronic pyelonephritis patients, 0.0% (0) alcoholics, 0.0% (0) cirrhotics, 1.6% (1) renal Tb patient, 9.7% (6) idiopathic and 56.5% (35)

Table 1

	AGE			SEX		ETHNIC ORIGIN		
	Mean age at diagnosis	Median age at diagnosis	Range	Male freq.	Female distribution	White freq.	Black distribution	Hisp.
All Patients (61)	39.9	37.0	10-18	30.6%	69.4%	48.41	48.4%	3.2%
Juvenile Diabetes (2)	21.0	20.5	20-22	-	100%	100%	-	-
Adult onset diab. (9)	56.1	57.0	47-65	33.3%	66.6%	66.6%	33.3%	-
SS-hemoglobinopathy (2)	41.5	39.0	37-46	50%	50%	-	100%	-
SA-hemoglobinopathy (14)	36.6	29.0	21-63	21.4%	78.6%	-	100%	-
SC-hemoglobinopathy (2)	20.5	20.5	20-21	50%	50%	-	100%	-
Analgesic Abuse (6)	39.1	42.5	20-52	16.7%	83.3%	66.7%	33.3%	-
Pharmacotherapeutic use of Analgesics (7)	47.8	45.0	26-70	42.9%	57.1%	42.9%	57.1%	-
Urinary tract obstruc.-Nephrolithiasis (17)	47.6	48.0	21-82	29.4%	70.6%	58.8%	29.4%	11.8%
Urinary tract obstruc.-intrinsic anomalies (12)	40.2	36.5	10-65	33.3%	66.7%	75.0%	25.0%	-
Chronic Pyelonephritis (21)	42.0	45.0	10-82	28.6%	71.4%	76.2%	19.0%	4.8%
Alcoholism (7)	48.6	46.0	36-63	57.1%	42.9%	14.3%	85.7%	-
Cirrhosis (4)	47.2	45.5	36-58	75.0%	25.0%	25.0%	75.0%	-
Renal TB (1)	21.0	21.0	-	-	100%	100%	-	-

Table 1. Demographic Description of Patients: All patients, patients grouped by Associated Conditions

mixed etiologies patients); and B- where patients were counted by number of times they appeared associated with a specific condition regardless of existence of other conditions for the same patient--same patients are thus included in different groups (distribution of patients in this manner is 17.7% (11) diabetics, 29.0% (18) S-hemoglobin patients, 21.0% (13) analgesic abusers, 46.8% (29) UT obstruction patients, 34.4% (21) chronic pyelonephritis patietns, 11.3% (7) alcoholics, 6.4% (4) cirrhotics, 1.6% (1) renal tuberculosis patient). Due to the large number of patients with mixed associated conditions and consequently the small number of patients that have only one associated condition we chose to use the latter method of grouping the patients for all other correlations.

Data collected as significant medical history for all 62 patients showed the following frequency distributions for diseases: cancer 8.1%, tuberculosis 4.8%, stroke 1.6%, neurologic disease 21.0%, other renal disease 14.5%, heart disease 17.7%, liver disease 8.1%, lung disease 16.1%, GI disease 21.0%, collagen vascular disease 0%, allergies 14.9%, psychiatric history 21.0% (13 patients, 11 of which had depression).

Of the 62 patients, only 13 or 21.0% were found to be hypertensives (10 with diastolics between 90 and 100, two between 100 and 110 and one between 110 and 140). Mean systolic pressure at initial presentation was 130 mmHg and the mean diastolic

pressure was 80 mmHg.

Forty-six percent (27) of patients did not smoke cigarettes, while 24.1% (14) were considered light smokers (less than one pack/day for more than one year) and 29.3% (17) were considered heavy smokders (more than one pack/day for more than one year).

Sixty-nine percent (43) of all patients had a history of urinary tract infection. E. Coli was the organism found in 16 patients, Klebsiella species in three patients, Proteus species in three patients, Gram + cocci in 1, mixed organisms in six, other organisms in three. Forty-seven percent (29) of all patients were actually found to have a urinary tract infection when the diagnosis of papillary necrosis was made.

Diagnosis was made by intravenous pyelography in 77.4% (48) of patients. Six patients--9.7% were diagnosed with a retrograde urographic exam. In five patients--8.1% diagnosis was stated in a pathological report at nephrectomy. In one patient diagnosis was made when a sloughed papilla was removed at surgery. In another patient diagnosis was made with the aid of a selective arteriogram. Still in another patient the diagnosis is stated in the surgeon's post-op note. None of the patients were diagnosed by tissue passed in the urine or at necropsy. Findings at diagnosis were certainly compatible with criteria for diagnosis renal papillary necrosis in 79.0% (49) of all patients and probably compatible in 21.0% (13).

Sixty-four percent (40) of all patients had unilateral involvement while 35.5% (22) had both kidneys involved. By associated conditions: diabetics--81.8% unilateral, 18.2% bilateral; S-hemoglobin--50% unilateral, 50% bilateral; analgesic abusers--61.5% unilateral, 38.5% bilateral; UT obstruction patients--69.0% unilateral, 31.0% bilateral; chronic pyelonephritis--61.9% unilateral, 38.1% bilateral; alcoholics--57.1% unilateral, 42.9% bilateral; cirrhotics--75% unilateral, 25% bilateral; the one patient with renal Tb had unilateral involvement.

Seventy-seven percent (48) of all patients received treatment for their renal papillary necrosis: 67.7% (42) antibiotics (29.0% Ampicillin, 17.7% Gentamicin, 16.1% a cephalosporin, 12.9% Gantirisin, 33.9% other); 40.3% (25) fluids; 17.7% (11) ureteral catheterization; 27.4% (17) surgery and 3.2% (2) dialysis.

Nineteen percent (12) of all patients are known to be dead. Mean years of follow-up since diagnosis for all patients was 5.2 years, median--4.0 years, range 0-14 years. Seven patients died of extrarenal causes (CVA, MI), one patient died in severe renal failure, four patients died of undetermined causes. Distribution of deaths among the associated conditions can be appreciated in Table 2.

Table 3 sums up the data available on renal function as de-

termined by mean serum creatinine at initial presentation and at years 1,2,3,4, and 5 after diagnosis.

Tables 4 and 5 display findings of urinalysis: Table 4 for all patients at initial presentation and at years 1,2,3, 4 and 5 after diagnosis; and Table 5 for all patients and for patients grouped by associated conditions at initial presentation only.

Tables 6 and 7 are similar to Tables 4 and 5 but they present findings of signs and symptoms instead.

For the hypertensives, their mean age was 47.6 years; 69.2% of them were females, 30.8% were males; 46.2% were White, 46.2% were Black and 7.6% Hispanic. Only one hypertensive patient is known to be dead and died of an extrarenal cause. Sixty-one percent of hypertensives smoked cigarettes and 84.6% had a history of urinary tract infections. Their mean serum creatinine at diagnosis was 2.3 mg/dl as compared to 1.6 mg/dl for the normotensive subgroup. Their mean serum creatinine for the years following diagnosis varies from 1.2 mg/dl to 1.4 mg/dl for years 1 to 4 after initial presentation (n less than 5 for all years) and rises to 3.8 mg/dl (n=2) five years after diagnosis. At initial presentation, 61.5% (8) of patients had pyuria, none had glucosuria, 30.8% (4) had proteinuria, 30.8% (4) had hematuria by U/A, 76.9% had bacteriuria, mean pH was 6.0, and mean specific gravity was 1.014. Twenty-three percent (3) of patients with hypertension

Table 2

	Percentage of Patients known to be dead	Mean Years Since Diagnosis
ALL PATIENTS (62)	19.4% (12)	5.2
DIABETES (11)	54.5% (6)	6.4
S - HEMO (18)	5.5% (1)	4.7
ANALGESIC ABUSE (18)	15.4% (2)	5.9
UT OBSTRUCTION (29)	13.8% (4)	5.5
CHRONIC PYELO. (21)	14.3% (3)	7.0
ALCOHOLISM (7)	0.0% (0)	2.1
CIRRHOSIS (4)	0.0% (0)	2.0
RENAL TB (1)	0.0% (0)	2.0

Table 2. Percentage of Patients known to be Dead:
All patients, patients grouped by Associated Conditions.
Mean years of follow-up for all Patients - 5.2 yrs.

Table 3

	MEAN SERUM CREATININE					
	At dx	At 1 yr	At 2 yrs	At 3 yrs	At 4 yrs	At 5 yrs
All Patients	1.8 (49)	1.9 (20)	1.4 (9)	2.3 (7)	1.6 (4)	3.1 (7)
Juvenile Diabetes	1.5 (1)	1.7 (1)	_	1.6 (1)	-	3.2 (1)
Adult onset DM	2.2 (9)	4.0 (4)	2.0 (1)	-	1.1 (1)	3.8 (2)
SS Hemoglobinopathy	0.8 (2)	-	-	-	-	-
SA Hemoglobinopathy	1.2 (10)	1.1 (4)	0.9 (3)	-	-	6.0 (1)
SC Hemoglobinopathy	1.0 (1)	-	-	-	-	-
Analgesic Abuse	2.6 (4)	3.5 (3)	1.9 (2)	-	-	1.3 (1)
Pharmacotherapeutic use of Analgesics	1.6 (5)	1.5 (3)	-	-	-	-
UT Obstruction-Nephrolithiasis	2.6 (14)	1.4 (5)	1.6 (2)	3.1 (3)	1.2 (2)	1.6 (3)
UT Obstruction-Intrinsic Anomalies	1.8 (10)	2.8 (4)	1.6 (3)	1.6 (1)	-	-
Chronic Pyelo	2.0 (20)	3.0 (7)	1.8 (4)	2.7 (5)	1.7 (3)	3.9 (4)
Alcoholsim	1.4 (6)	1.3 (3)	1.2 (3)	-	-	-
Cirrhosis	1.3 (4)	1.2 (2)	-	-	-	-
Renal TB	-	-	-	-	-	-

Table 3. Renal Function at Diagnosis and at 1,2,3,4 and 5 years after diagnosis for All Patients, Patients grouped by associated conditions.

Table 4

	(61) Diagnosis	(28) 1 yr	(16) 2 yrs	(12) 3 yrs	(4) 4 yrs	(10) 5 yrs
Pyuria	62.3% (38)	46.4% (13)	56.2% (9)	66.7% (8)	75.0% (3)	50.0% (5)
Glucosuria	11.5% (7)	14.3% (4)	12.5% (2)	8.3% (1)	25.0% (1)	30.0% (3)
Proteinuria	41.0% (25)	32.3% (9)	43.8% (7)	58.3% (7)	50.0% (2)	50.0% (5)
Hematuria	41.0% (25)	17.9% (5)	18.8% (3)	33.3% (4)	50.0% (2)	30.0% (3)
Bacteriuria	75.4% (46)	55.6% (15)	68.8% (11)	58.3% (7)	100.0% (4)	70.0% (7)
Mean pH	6.0	6.1	6.3	6.1	5.6	5.8
Mean SG	1.015	1.015	1.016	1.015	1.016	1.015
% SG $\leq$ 1.015	61.7%	57.7%	60.0%	54.5%	50.0%	60.0%

Table 4. Findings of Urinalysis at Diagnosis and at 1,2,3,4 and 5 years after diagnosis for all Patients. (Pyuria = any in males, 5 wbc's in females, glucosuria = $\geq$ 1+, proteinuria = $\geq$ 1+, hematuria = $>$ 5 rbc's/HPF, bacteriuria = any /HPF.).

Table 5

	Pyuria	Glucos-uria	Protein-uria	Hema-turia	Bacteri-uria	Mean pH	Mean SG	% SG ≤1.015
ALL PATIENTS (61)	62.3% (38)	11.5% (7)	41.0% (25)	41.0% (25)	75.4% (46)	6.0	1.015	61.7%
DIABETES (10)	80.0% (8)	60.0% (6)	60.0% (6)	50.0% (5)	70.0% (7)	5.8	1.015	40.0%
S-HEMOGLOBIN (18)	44.4% (8)	0.0% (0)	44.4% (8)	44.4% (8)	61.1% (11)	5.9	1.012	70.6%
ANALGESIC ABUSE (13)	53.8% (7)	15.4% (2)	38.4% (5)	53.8% (7)	84.6% (11)	6.1	1.015	69.2%
UT OBSTRUCTION (29)	69.0% (20)	13.8% (4)	48.3% (14)	51.7% (15)	79.3% (23)	6.2	1.014	57.1%
CHRONIC PYELO (21)	76.2% (16)	14.3% (3)	52.4% (11)	47.6% (10)	81.0% (17)	6.2	1.014	66.7%
ALCOHOLISM (7)	42.9% (3)	0.0% (0)	42.9% (3)	42.9% (3)	71.4% (5)	6.2	1.016	33.3%
CIRRHOSIS (4)	75.0% (3)	0.0% (0)	25.0% (1)	25.0% (1)	100.0% (4)	6.0	1.014	50.0%
RENAL TB (1)	No	No	No	No	Yes	5.0	1.021	--

Table 5. Findings of urinalysis at Diagnosis - Initial Presentation for all patients, for patients grouped by associated conditions

Table 6

	(61) Diagnosis	(31) 1 yr.	(19) 2 yrs.	(14) 3 yrs.	(7) 4 yrs.	(11) 5 yrs.
Assymptomatic	23.0% (14)	65.6% (21)	68.4% (13)	35.7% (5)	28.6% (2)	36.4% (4)
Dysuria	16.4% (10)	6.4% (2)	10.5% (2)	21.4% (3)	0.0% (0)	9.1% (1)
Frequency	18.0% (11)	6.4% (2)	0.0% (0)	14.3% (2)	14.3% (1)	9.1% (1)
Polyuria	3.3% (2)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Nocturia	14.8% (9)	3.2% (1)	0.0% (0)	14.3% (2)	28.6% (2)	9.1% (1)
Hematuria	32.8% (20)	9.7% (3)	5.6% (1)	28.6% (4)	14.3% (1)	9.1% (1)
Flank or back pain	49.2% (30)	12.9% (4)	11.1% (2)	28.6% (4)	42.9% (3)	36.4% (4)
Hypertension	18.0% (11)	6.4% (2)	16.7% (3)	7.1% (1)	14.3% (1)	18.2% (2)
Renal Tenderness	29.5% (18)	3.2% (1)	5.6% (1)	21.4% (3)	28.6% (2)	27.3% (3)
Dehydration	6.6% (4)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Fever (T 101° F)	38.0% (19)	3.2% (1)	5.6% (1)	21.4% (3)	14.3% (1)	18.2% (2)

Table 6. Signs and Symptoms at Diagnosis and at 1,2,3,4 and 5 yrs after diagnosis for all Patients.

Table 7

	Assympto-matic	Dys-uria	Fre-quency	Poly-uria	Noc-turia	Hema-turia	Flank or back pain	Hyper-tension	Renal tender-ness	Dehyd-ration	Fever
All Patients (61)	23.0% (14)	16.4% (10)	18.0% (11)	3.3% (2)	14.8% (9)	32.8% (20)	49.2% (30)	18.0% (11)	29.5% (18)	6.6% (4)	38.0% (19)
Diabetes (10)	20.0% (2)	0.0% (0)	10.0% (1)	10.0% (1)	10.0% (1)	20.0% (3)	30.0% (3)	10.0% (1)	30.0% (3)	20.0% (2)	50.0% (5)
S-Hemoglobin (18)	38.9% (7)	16.7% (3)	27.8% (5)	5.6% (1)	16.7% (3)	50.0% (9)	44.4% (8)	22.2% (4)	11.1% (2)	0.0% (0)	16.7% (3)
Analgesic Abuse (13)	0.0% (0)	30.8% (4)	46.2% (6)	0.0% (0)	46.2% (6)	53.8% (7)	61.5% (8)	23.1% (3)	38.5% (5)	7.7% (1)	30.8% (4)
UT Obstruction (29)	24.1% (7)	17.2% (5)	13.8% (4)	3.4% (1)	20.7% (6)	31.0% (9)	55.2% (16)	20.7% (6)	44.8% (13)	10.3% (3)	48.3% (14)
Chronic Pyelo (21)	28.6% (6)	19.0% (4)	14.3% (3)	0.0% (0)	9.5% (2)	14.3% (3)	47.6% (10)	23.8% (5)	28.6% (6)	4.8% (1)	42.8% (9)
Alcoholism (7)	42.9% (3)	28.6% (2)	14.3% (1)	0.0% (0)	14.3% (1)	28.6% (2)	28.6% (2)	42.9% (3)	14.3% (1)	14.3% (1)	14.3% (1)
Cirrhosis (4)	50.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)	25.0% (1)	0.0% (0)	25.0% (1)	50.0% (2)	0.0% (0)	0.0% (0)	0.0% (0)
Renal TB (1)	Yes	No	No	No	No	No	No	No	No	No	No

Table 7. Signs and Symptoms at Diagnosis - Initial Presentation for ALL PATIENTS, for patients grouped by associated conditions

and papillary necrosis were asymptomatic at diagnosis, 23.1% (3) had dysuria, 15.4% (2) had frequency, none had polyuria, 23.1% (3) had nocturia, 15.4% (2) had hematuria as a symptom, 38.5%(5) had flank or back pain, 15.4% had renal tenderness, 7.7% (1) had dehydration and 38,5% (5) had temperatures above 101°F.

For those patients with renal papillary necrosis who smoked cigarettes their renal function was determined and compared to that of the non-smokers--mean serum creatinine at diagnosis: non-smokers--1.6 mg/dl, light smokers--1.4 mg/dl, heavy smokers-2.4 mg/dl. For the next five years after diagnosis mean serum creatinine ranged between 1.1 mg/dl and 1.9 mg/dl for non-smokers, between 1.5 mg/dl and 6.0 mg/dl for light smokers and between 1.3 mg/dl and 4.0 mg/dl for heavy smokers.

For those patients with a history of urinary tract infection, their mean age was 42.7 years, 74.4% were females and 25.6% males; 62.8% were White, 34.9% Black, 2.3% Hispanic. Eight of the 12 patients known to be dead had urinary tract infection history. Their mean serum creatinine at diagnosis was 2.0 mg/dl as compared to 1.0 mg/dl for those patients who did not have a history of UTI. For the next five years after diagnosis their mean serum creatinine ranged between 1.5 mg/dl and 3.1 mg/dl. At initial presentation, 73.8% (31) had pus cells in the urine, 16.7% (7) had glucosuria, 47.5% (20) had proteinuria, 42.9% (18) had hema-

turia by U/A, 76.2% (32) had bacteriuria, mean pH was 6.0 and mean specific gravity 1.014. Nineteen percent had dysuria, 21.4% had frequency, 2.4% had polyuria, 16.7% had nocturia, 26.2% had hematuria as a symptom, 54.8% had flank or back pain, 21.4% had hypertension, 38.1% had renal tenderness, 9.5% were dehydrated and 45.2% had a temperature above 101°F. Eighty-eight percent (38) of these patients received antibiotics for treatment at their initial presentation with papillary necrosis.

Among patients that received any treatment during initial presentation, nine deaths are known--18.8%. From the non-treated group three patients are known to be dead--21.4%. Mean serum creatinine at diagnosis was 1.9 mg/dl for those who received treatment, and 1.1 mg/dl for those that were not treated. For those treated, mean serum creatinine at one year--2.3 mg/dl (14), at two years 1.4 mg/dl (9), at three years--2.5 mg/dl (6), at four years--1.6 mg/dl (4) and at five years--3.1 mg/dl (7).

The variable that ascertains certainty of diagnosis was correlated with occurence of associated conditions: 91.8% (45) of those whose diagnosis is said to be certain do have one or more of the conditions known to be associated with papillary necrosis; 76.9% (10) of those with a probable diagnosis do have associated conditions also. A certain diagnosis was definite documentation of the disease by X-rays and/or histology; while a probable one lacked this documentation. The mean serum creatinine

at diagnosis for those with a certain diagnosis was 1.9 mg/dl while it was 1.4 mg/dl for those with a probable one. Mean serum creatinine during the five years of follow-up was always lower for the probable group than for the certain group.

Table 8 illustrates incidences of the different associated conditions in the major studies in the literature. Our group had a more varied distribution of associated conditions.

Table 8

ASSOCIATED CONDITIONS	Liverpool study (18) 31 patients	Denmark study (39) 66 patients	Cleveland Cl.study (56) 14 patients	Yale-New Haven 1977 study [illegible] 62 patients
Diabetes	22%	8%	21%	18%
S-hemoglobin	-	-	-	29%
Analgesic abuse	16%	79%	28%	21%
UT obstruction	29%	12%	28%	47%
Pyelone-phritis	-	-	100%	34%
Alcoholism	-	-	-	11%
Cirrhosis	-	-	-	6%
Renal TB	3%	-	-	2%
Uncertain	35%	-	-	10%
Mixed	6%	-	100%	56%

Table 8. Comparison of frequency distributions for the different associated conditions in the major studies in the literature and our study.

Discussion

Most of our results stand by themselves in their descriptive importance. Let us consider first the distribution of patients among the different associated conditions. It is indeed remarkable that 56% of our patients had more than just one condition associated with papillary necrosis. At least two implications are derived from this observation: 1--associated conditions when present simultaneously may have additive effects in the pathogenesis of the papillary lesion, presumably by further damaging the vascular supply to the area, thus making papillary necrosis in these patients more common than in those with only one etiologic factor; and 2--the presence of one associated condition may predispose to the occurrence of another, specifically chronic pyelonephritis resulting from long standing urinary tract obstruction or diabetes mellitus. If we consider that chronic pyelonephritis and urinary tract obstruction were found in association in 14 patients, both of the above mentioned postulates may be correct.

Only one out of the 13 analgesic-abuse patients did not have another associated condition. This finding supports the observation that papillary necrosis caused by analgesic abuse is not as common here as in some other countries (51). Also of interest is the fact that only two out of 21 patients with chronic pyelonephritis in this study had chronic pyelonephritis as the only associated condition, suggesting that chronic pyelonephritis may

be secondary or simultaneous to papillary necrosis caused by other conditions. Still, the two patients with chronic pyelonephritis alone agree with the case reports of papillary necrosis where chronic pyelonephritis is the only associated condition (42). It is important also to note that alcoholism and cirrhosis did not present alone in any of these patients. However, one patient had both alcoholism and cirrhosis as the only associated conditions to his papillary necrosis which supports Longacre's association of cirrhosis of the liver and renal papillary necrosis (62).

When arranged from most common to least common, associated conditions appear as follows: urinary tract obstruction, chronic pyelonephritis, S-hemoglobin, analgesic abuse, diabetes, alcoholism, cirrhosis and renal Tb.

The demographic data shows that the typical patient with papillary necrosis is middle aged; females more than twice as common as males. No ethnic group seemed to be more particularly affected, except in the S-hemoglobin patients who were 100% Black. It is interesting to note that the youngest (10 y.o.) and the oldest (82 y.o.) patients both had urinary tract obstruction and chronic pyelonephritis which suggests that papillary necrosis can occur in this setting at any age. The analgesic abuse patients were mostly White females, an observation that agrees with other reports in the literature (39). The oldest subgroup of patients was the adult-onset diabetes with a mean age of 56.1 years (16

years above the mean age for all patients), which correlates well with the higher mortality of diabetics in this study.

Most commonly, diagnosis was arrived at with intravenous pyelography, which reflects the utility of this radiographic exam in the search of this disease. The fact that none of our patients were diagnosed by observing tissue passed in the urine implies that either it is not a common feature (in fact only one of our patients passed some papillary tissue in the urine) or that straining the urine of these patients is not a most suitable way for arriving at diagnosis.

Unilateral involvement was found to be twice as common as disease in both kidneys. The S-hemoglobin patients, however, were distributed equally between unilateral and bilateral involvement. Why unilateral involvement is more common and why do some patients have unilateral and others bilateral disease, we can not explain.

At least 19% of all patients are known to be dead after a mean of 5.2 years of follow-up after initial presentation. Not surprisingly, half of the patients who died were diabetics. This observation agrees with the reports in the literature that attribute a bad prognosis to diabetes when associated with papillary necrosis (1,39,88). Fifty-four percent of our diabetic patients are known to be dead after a mean of 6.4 years of follow-up after diagnosis, which makes this group the highest in mortality. In interpreting this result, two other observations should be taken into account:

this group of patients was also the oldest of all groups, and secondly, the pathology of such kidneys may include other renal injuries such as glomerulosclerosis and chronic pyelonephritis as well (88).

We were not able to do a survivalship table since we did not have available all the information it takes to make one, specifically the dates of death for all patients who died. Our mortality numbers reflect only a minimum of patients known to be dead, and the assumption that all other patients are still alive can not be guaranteed since our attempt to update follow-up on all live patients did not have a satisfactory yield. With this in mind, Table 2 implies that short term prognosis of renal papillary necrosis may be generally benign for all associated conditions except for diabetes, which we have already discussed. When cause of death was determined, extrarenal causes like cerebrovascular accidents and myocardial infarction were most commonly found (in fact, we know of only one patient who died in severe renal failure).

Determination of renal function was made by means of the serum creatinine values where 1.5 mg/dl was defined as upper limit of normal. At the time of diagnosis of papillary necrosis, most patients in our group did not have any degree of renal insufficiency (median = 1.4 mg/dl, 61% of all patients had serum creatinines of 1.5 mg/dl or less) even when mean serum creatinine was 1.8 mg/dl. One year after diagnosis, the nean serum creatinine remains basically

unchanged but the number of patients who had such determination decreased by more than one half. Unfortunately, when we look throughout Table 3 for information on the renal function of these patients, we find that number of patients followed with serum creatinines decreased considerably with time. Apparently, only those patients with serious problems or elevated creatinines had their renal function evaluated. As a result of this, the sample of patients is extremely biased and we don't believe we can reach at any further conclusion about renal function from this data.

It is interesting to note that 62% of all patients had pyuria at initial presentation; the associated condition in which it was most common was diabetes (80%), very closely followed by the chronic pyelonephritis patients (76%). Pyuria was defined as more than 5wbc's/HPF. Among the patients who had urinalysis in the next five years, pyuria persisted as a fairly common finding. Our renal Tb patient did not have sterile pyuria, but instead had bacteriuria and no pus cells in the urine. She did not have a bacterial infection and was asymptomatic at diagnosis.

Only 11.5% of all patients had glucosuria ($\geq$1+) and this finding was most common among diabetics (60%). Forty-one percent of all patients had proteinuria (more than trace) at diagnosis, and diabetes again was the associated condition in which it was most common (60%) closely followed by chronic pyelonephritis (52%) and UT obstruction (48%). Once again, among the patients who had further U/A's, proteinuria was noted to persist as a common finding.

Interestingly, hematuria (>5 rbc's/HPF) was noted in 41% of all patients and all associated conditions seemed about equally affected with this finding, with the exception of our renal Tb patient who did not present with hematuria. A general trend of decrease in number of patients with hematuria can be observed in the years of follow-up, particularly the drop from 41% at diagnosis to 18% one year later. This drop in number of patients with hematuria at follow-up is certainly reassuring.

Bacteriuria (any bacteria/HPF) was observed in 75% of all patients at diagnosis. It was a common finding in all the associated conditions and persisted throughout follow-up.

Mean specific gravity for all patients was 1.015, exactly the value we defined beforehand as the lower limit of adequate concentration ability. Since we do not know the hydration status of these patients (except that 7% of them were clinically dehydrated at initial presentation) we cannot say anything definite about their concentration ability. However, we can note that most patients (62%) had specific gravities less than or equal to 1.015 at diagnosis and that the mean SG did not change during follow-up. This trend was most obvious in the S-hemoglobin patients who had a mean SG at diagnosis of 1.012, which agrees with observations made in the literature (83). No significant aberrations were noted in the mean pH values for all patients and all groups of patients.

Almost one fourth of all patients were asymptomatic during

initial presentation, an interesting finding which suggests that the clinical picture of this disease can be silent at least until complications from the papillary necrosis occur. If we consider that our patient selection was in itself a biased procedure since only patients who seeked medical attention make our entire group, we must realize that papillary necrosis might very well be common in its undiagnosed, uncomplicated form. Interestingly enough, none of our analgesic abusers were asymptomatic.

As can be seen in Table 6, the proportion of patients with signs and symptoms including dysuria, frequency, polyuria, nocturia, hematuria, flank or back pain, hypertension, renal tenderness, dehydration and fever, did fall substantially during follow-up. This may speak in favor of a good prognosis for most patients in terms of signs and symptoms. Interestingly, 36% of patients seen five years after diagnosis had flank or back pain and 27% had renal tenderness. These were the clinical signs most salient at five years (when only 11 out of the 62 patients were seen) which indicate an acute renal presentation for the affected patients.

During initial presentation, flank or back pain was the most common symptom (49%) and 38% had a temperature equal or greater than 101°F, again indicating an acute presentation. Gross hematuria was the third most common symptom (33%). The difference between hematuria observed by U/A and hematuria recorded as a symptom gives us an indication of the patients with microscopic hematuria = five patients or 8%.

Polyuria was a most rare symptom--only two patients and at least one was a diabetic.

Thirteen out of 18 patients with renal tenderness and 14 out of the 19 patients with temperatures of 101°F or above had urinary tract obstruction, an observation that seems to link the acute presentation of the disease with this associated condition.

Only 21% of all patients were found to have diastolic pressures of 90 mmHg or above so we are unable to suggest a strong association between papillary necrosis and elevated blood pressure. Interestinly, 85% of the hypertensive patients had had a urinary tract infection at some time. They also had a greater degree of renal insufficiency at diagnosis than the normotensive group. However, the fact that only one of the patients known to be dead had hypertension (and died of an extrarenal cause), and the observation that mean serum creatinines ranged in between 1.2 mg/dl and 1.4 mg/dl for the next four years after diagnosis suggest that hypertension does not carry bad prognostic implications when it occurs together with papillary necrosis. From our data we could not determine if hypertension was a consequence of papillary necrosis or merely simultaneous. However, the fact that its frequency fell from 18% to 6% one year after diagnosis when we still had a considerable number of patients, seems to indicate that it is more a part of the acute or initial presentation when the patient is symptomatic. Their substantial fall in mean serum creatinine also indicates that these patients were suffering an acute renal disease probably accom-

panied by acute obstruction or infection.

For the 53% of patients who smoked cigarettes, their initial renal function was found to be slightly worse than that of non-smokers. Heavy smokers did have a substantially elevated mean serum creatinine (2.4) at diagnosis when compared to that of the non-smokers (1.6). This suggests that cigarette smoking may be related to decreased renal function in this setting; and in general, smokers had greater values for mean serum creatinines during follow-up.

In agreement with those investigators who found infection to be a common denominator among most patients with papillary necrosis (28,56,57), we found a strong association between renal papillary necrosis and history of urinary tract infection. Sixty-nine percent of our patients had had a urinary tract infection at some time and 47% of them were actually infected at initial presentation. Their mean serum creatine at diagnosis was twice the value for those who did not have a history of infection, and most significantly eight of the 12 dead patients had a urinary tract infection history. Not only does infection seem to be very common among papillary necrosis patients, but the data also suggests that it may worsen the prognosis of the disease.

Seventy-seven percent of patients received some type of treatment for their papillary necrosis during initial presentation and among them nine deaths are known (19%). A similar frequency distribution of deaths was noted for the non-treated group (21%), which

indicates that treatment did not make much of a difference in the mortality of this disease, which is not unexpected since treatment was not directed towards the pathogenesis of papillary necrosis.

Conclusions

More than half of the patients in this study had more than just one associated condition to their papillary necrosis. These conditions appeared associated with papillary necrosis in the following order of frequency: urinary tract obstruction, chronic pyelonephritis, S-hemoglobin, analgesic abuse, diabetes, alcoholism, idiopathic, cirrhosis and renal tuberculosis. Intravenous pyelography was still the most common way of arriving at diagnosis. Finding of papillary tissue in the urine was a rare feature and probably not a suitable means of diagnosis. Unilateral involvement was twice as common as bilateral disease in our patients.

Short term prognosis of renal papillary necrosis in terms of mortality may be generally benign for all groups except for diabetics, who also were the oldest group. At initial presentation, most patients did not have any degree of renal insufficiency. One year after diagnosis, mean serum creatinine remained basically unchanged. Any other conclusions about renal function in the next five years cannot be made because of inadequate follow-up.

Pyuria and proteinuria were common findings for all patients but more commonly for diabetics and patients with chronic pyelonephritis. These findings both persisted throught the five years of follow-up. Hematuria (by U/A) was common in all condiitons except renal Tb (one patient) and its frequency fell considerably after initial presentation. Microscopic bacteriuria was common in

all conditions and persisted throughout follow-up.

One fourth of all patients were asymptomatic at diagnosis. Frequency of signs and symptoms among all patients fell substantially during follow-up suggesting good prognostic implications. Dysuria and frequency were most common among the analgesic abuse group. Flank or back pain, fever and gross hematuria were the most common signs and symptoms for all patients which point towards an acute presentation. Most of the patients with renal tenderness and fever had urinary tract obstruction which links the acute presentation with this associated condition.

Hypertension was not found in strong association to renal papillary necrosis and does not carry serious prognostic implications. High blood pressure is probably part of the acute or initial presentation when the patient is symptomatic.

A strong association was found between infection and renal papillary necrosis. History of urinary tract infection is an isolated variable that appears to worsen prognosis. Treatment did not make much of a difference in mortality of this disease.

Perhaps the most important conclusion of this study is the realization that nothing definite can be said about prognosis and natural history of this disease until a prospective study is done. We have only presented data on the clinical features and short term follow-up of these patients with the limitations that accompany a retrospective study. Our results on known mortality, renal

function, U/A findings and signs and symptoms make us believe that renal papillary necrosis is not such a bad disease after all. Definite proof will be provided when this question is studied prospectively.

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Card 1

Patient number	_ _ _	(1-3)
Card number	_	(4)
Unit number	_ _ _ _ _ _ _	(5-11)
Age at diagnosis	_ _	(12-13)
Current age	_ _	(14-15)
Sex 0=male 1=female	_	(16)
Ethnic origin 0=Caucasian 1=Black 2=Hispanic 3=Oriental 4=Other	_	(17)
Dead (=0) or Alive (=1)	_	(18)
Cause of death 0=renal 1=extrarenal	_	(19)
Associated conditions 0=yes 1=no	_	(20)
Diabetes mellitus - juvenile	_	(21)
Adult onset diabetes mellitus	_	(22)
Sickle hemoglobinopathies	_	(23)
SS	_	(24)
SA	_	(25)
SC	_	(26)
Analgesic abuse syndrome	_	(27)
Depression	_	(28)
GI bleeding	_	(29)
Peptic ulcer	_	(30)
ASA daily consumption	_ _ _	(31-33)
Phenacetin daily	_ _ _	(34-36)
Other analgesic	_	(37)
Urinary tract obstruction	_	(38)
Nephrolithiasis	_	(39)
Intrinsic anomalies	_	(40)
Chronic pyelonephritis	_	(41)
Renal vein thrombosis	_	(42)
Alcoholism	_	(43)
Cirrhosis	_	(44)
Pharmacotherapeutic use of analgesics	_	(45)

Significant Medical History 0=yes, 1=no _ (46)

Cancer _ (47)

Tuberculosis _ (48)

Stroke _ (49)

Neurologic disease _ (50)

Other kidney disease _ (51)

Heart disease _ (52)

Liver disease _ (53)

Lung disease _ (54)

Stomach or bowel disease _ (55)

Collagen vascular disease _ (56)

Allergies _ (57)

Psychiatric history _ (58)

- Depression _ (59)
- Schizophrenia _ (60)
- Manic depressive _ (61)
- Other psychoses _ (62)
- Other neuroses _ (63)

Hypertension _ (64)

0=none
1=diastolic 90-100
2=diastolic 100-110
3=diastolic 110-140
4=diastolic 140&up

Blood pressure on admission : ___/___ (65-70)

Cigarette smoking _ (71)

0=none
1=less than 1 pack/day for ≥ 1 yr.
2=more than 1 pack/day for ≥ 1 yr.

History of urinary tract infections (including pyelonephritis) 0=yes 1= no _ (72)

Number of recurrences __ (73-74)

Organisms isolated by culture (more than 100,000 colonies) _ (75)

0=E. Coli
1=Klebsiella
2=Proteus
3=Pseudomonas
4=Gram+ cocci
5=Mixed 6=other

Subsequent infections _ (76)

0=same bugs
1=different bugs
2=same and different
3= unknown

Treatment of UTI 0=no treatment 1=antibiotic with resolution 2=antibiotic without resolution 3=antibiotic without follow up 4= suppressive therapy	—	(77)
	BLANK	(78-80)

Card 2

Patient number	_ _ _	(1-3)
Card number	_	(4)
Date of diagnosis	_ _/_ _	(5-8)
No. of months since dx.	_ _	(9-10)
Diagnosis made 0=radiologically - IVP 1=radiologically - Retrograde 2=path report - nephrectomy 3=path report - tissue passed in the urine 4=path report at autopsy	_	(11)
Certainty of diagnosis 0=findings certainly compatible with Renal Papillary Necrosis 1=findings probably compatible with Renal Papillary Necrosis	_	(12)
Renal Papillary Necrosis 0=unilateral 1=bilateral	_	(13)

Urinalysis at diagnosis 0=yes 1=no (admission U/A)

Pyuria (any-male, > 5-female wbc's/HPF)	_	(14)
Glucosuria (≥1+)	_	(15)
Proteinuria (no. of +'s)	_	(16)
Hematuria (> 5 rbc's/HPF)	_	(17)
Bacteriuria (any/HPF)	_	(18)
pH	_ _	(19-20)
Specific Gravity	_ _ _ _	(21-24)

Urinalysis 1 year after diagnosis

Pyuria	_	(25)
Glucosuria	_	(26)
Proteinuria	_	(27)
	_	(28)

Hematuria	-	(29)
Bacteriuria	-	(30)
pH	- -	(31-32)
S G	- - - -	(33-36)
Urinalysis 2 years after dx.	-	(37)
Pyuria	-	(38)
Glucosuria	-	(39)
Proteinuria	-	(40)
Hematuria	-	(41)
Bacteriuria	-	(42)
pH	- -	(43-44)
S G	- - - -	(45-48)
Urinalysis 3 years after dx.	-	(49)
Pyuria	-	(50)
Glucosuria	-	(51)
Proteinuria	-	(52)
Hematuria	-	(53)
Bacteriuria	-	(54)
pH	- -	(55-56)
S G	- - - -	(57-60)
Urinalysis 4 years after dx.	-	(61)
Pyuria	-	(62)
Glucosuria	-	(63)
Proteinuria	-	(64)
Hematuria	-	(65)
Bacteriuria	-	(66)
pH	- -	(67-68)
S G	- - - -	(69-72)
	BLANK	(73-80)

Card 3

Patient number	- - -	(1-3)
Card number	-	(4)

Urinalysis 5 years after dx.	_	(5)
Pyuria	_	(6)
Glucosuria	_	(7)
Proteinuria	_	(8)
Hematuria	_	(9)
Bacteriuria	_	(10)
pH	_ _	(11-12)
S G	_ _ _ _	(13-16)
BUN at diagnosis	_ _	(17-18)
BUN 1 year after dx.	_ _	(19-20)
BUN 2 years after dx.	_ _	(21-22)
BUN 3 years after dx.	_ _	(23-24)
BUN 4 years after dx.	_ _	(25-26)
BUN 5 years after dx.	_ _	(27-28)
Creatinine at diagnosis	_ _	(29-30)
Creatinine 1 year after dx.	_ _	(31-32)
Creatinine 2 years after dx.	_ _	(33-34)
Creatinine 3 years after dx.	_ _	(35-36)
Creatinine 4 years after dx.	_ _	(37-38)
Creatinine 5 years after dx..	_ _	(39-40)

Degree of renal insufficiency

0=creatinine less than 1.5
1=creatinine between 1.5 & 3.0
2=creatinine between 3.1 & 6.0
3=creatinine higher than 6.0

At diagnosis	_	(41)
1year after dx.	_	(42)
2 years after dx.	_	(43)
3 years after dx.	_	(44)
4 years after dx.	_	(45)
5 years after dx.	_	(46)
Creatinine clearance at diagnosis	_ _ _	(47-49)
Creatinine clearance 1 year later	_ _ _	(50-52)
Creatinine clearance 2 years later	_ _ _	(53-55)
3 years later	_ _ _	(56-58)
4 years later	_ _ _	(59-61)
5 years later	_ _ _	(62-64)

IVP or Retrograde description at dx. _ (65)

0=normal
1=necrosis in situ
2=medullary type
3=papillary type
4=not available

Number of calyces involved _ (66)

Subsequent IVP's

0=not done
1=no change
2=progressive changes
3=unrelated changes

1 year after dx. _ (67)
2 years after dx. _ (68)
3 years after dx. _ (69)
4 years after dx. _ (70)
5 years after dx. _ (71)

Signs & Symptoms at diagnosis 0=yes, 1=no _ (72)

Assymptomatic _ (73)
Dysuria _ (74)
Frequency _ (75)
Polyuria _ (76)
Nocturia _ (77)
Hematuria _ (78)
Flank or back pain _ (79)
Hypertension _ (80)

Card 4

Patient number ___ (1-3)
Card number _ (4)
Renal tenderness _ (5)
Dehydration _ (6)
Fever (in °F) ____ (7-10)

Signs and Symptoms 1 year after dx. _ (11)
Assymptomatic _ (12)
Dysuria _ (13)
Frequency _ (14)
Polyuria _ (15)
Nocturia _ (16)

Hematuria _ (17)
Flank or back pain _ (18)
Hypertension _ (19)
Renal tenderness _ (20)
Dehydration _ (21)
Fever _ _ _ _ (22-25)

Signs & Symptoms 2 years after dx. _ (26)
Assymptomatic _ (27)
Dysuria _ (28)
Frequency _ (29)
Polyuria _ (30)
Nocturia _ (31)
Hematuria _ (32)
Flank or back pain _ (33)
Hypertension _ (34)
Renal tenderness _ (35)
Dehydration _ (36)
Fever _ _ _ _ (37-40)

Signs & Symptoms 3 years after dx. _ (41)
Assymptomatic _ (42)
Dysuria _ (43)
Frequency _ (44)
Polyuria _ (45)
Nocturia _ (46)
Hematuria _ (47)
Flank or back pain _ (48)
Hypertension _ (49)
Renal tenderness _ (50)
Dehydration _ (51)
Fever _ _ _ _ (52-55)

Signs & Symptoms 4 years after dx. _ (56)
Assymptomatic _ (57)
Dysuria _ (58)
Frequency _ (59)
Polyuria _ (60)
Nocturia _ (61)

Hematuria	_	(62)
Flank or back pain	_	(63)
Hypertension	_	(64)
Renal tenderness	_	(65)
Dehydration	_	(66)
Fever	_ _ _ _	(67-70)
Signs & Symptoms 5 years after dx.	_	(71)
Assymptomatic	_	(72)
Dysuria	_	(73)
Frequency	_	(74)
Polyuria	_	(75)
Nocturia	_	(76)
Hematuria	_	(77)
Flank or back pain	_	(78)
Hypertension	_	(79)
Renal tenderness	_	(80)
Card 5		
Patient number	_ _ _	(1-3)
Card number	_	(4)
Dehydration	_	(5)
Fever	_ _ _ _	(6-9)
Treatment 0=yes, 1=no	_	(10)
Antibiotics	_	(11)
1.	_	(12)
2.	_	(13)
3.	_	(14)
4.	_	(15)
5.	_	(16)
Fluids	_	(17)
Ureteral cath	_	(18)
Surgery	_	(19)
Dialysis	_	(20)

CURRENT STATUS (Prospective Part I) 0=yes 1=no _ (21)

At present time, does the pt. have

symptoms ? _ (22)
dysuria ? _ (23)
frequency ? _ (24)
polyuria ? _ (25)
nocturia ? _ (26)
hematuria ? _ (27)
flank or back pain ? _ (28)
hypertension ? _ (29)
renal tenderness ? _ (30)
dehydration ? _ (31)
fever ? _ _ _ _ (32-35)

Do the associated conditions persist ? _ (36)

0

Prospective Part II

Present U/A : pyuria _ (37)
glucosuria _ (38)
proteinuria _ (39)
hematuria _ (40)
bacteriuria _ (41)
pH _ _ (42-43)
S G _ _ _ _ (44-47)

Present serum creatinine _ _ (48-49)
Present BUN _ _ (50-51)
Present creat clearance _ _ _ (52-54)
Present urine culture (0=negative, 1=E. Coli, 2=Klebsiella, 3=Proteus, 4=Pseudomonas, 5=G+ cocci, 6=mixed, 7=other, 8=not done) _ (55)
Present IVP or Retrograde 0=not done 1=no change 2=progressive changes 3=unrelated changes _ (56)
Blood pressure _ _ _ / (57-59)
_ _ _ (60-62)

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